Vectibix® (panitumumab) Accelerated Approval Status

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Oncologic Drug Advisory Committee Meeting
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Agenda

Overview of Vectibix® (panitumumab) Accelerated Approval and Status

Paul Eisenberg, MD, MPH
Global Regulatory Affairs & Safety, Amgen Inc.

Additional Amgen Attendees

David Chang, MD, PhD
Global Development

Jeff Wiezorek, MD
Global Development

Steven Galson, MD, MPH
Global Regulatory Affairs & Safety

Steve Snapinn, PhD
Global Biostatistics

Alan Rong, PhD
Global Biostatistics

Unmet Medical Need in Colorectal Cancer (CRC)

- In the US, over 140,000 patients will be diagnosed with CRC resulting in over 50,000 deaths annually[1-2]
  - 19% of patients with CRC have metastatic disease at diagnosis
  - 50% of patients treated for early stage CRC will develop metastases
  - 5 year survival rate of mCRC is ~10%
- Drugs approved for the treatment of mCRC
  - Chemotherapeutic agents: 5-FU, Eloxatin®, Camptosar®, Xeloda®
  - Biologic agents: Avastin®, Erbitux®, Vectibix®
- Erbitux® and Vectibix® are the only approved treatments for chemorefractory mCRC

1. Jemal A, et al. *CA Cancer J Clin.* 2010;60(5):277-300.
2. Altekruse SF, et al. SEER Cancer Statistics Review, 1975-2007, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2007/, based on November 2009 SEER data submission, posted to the SEER web site, 2010.

Vectibix® (panitumumab)

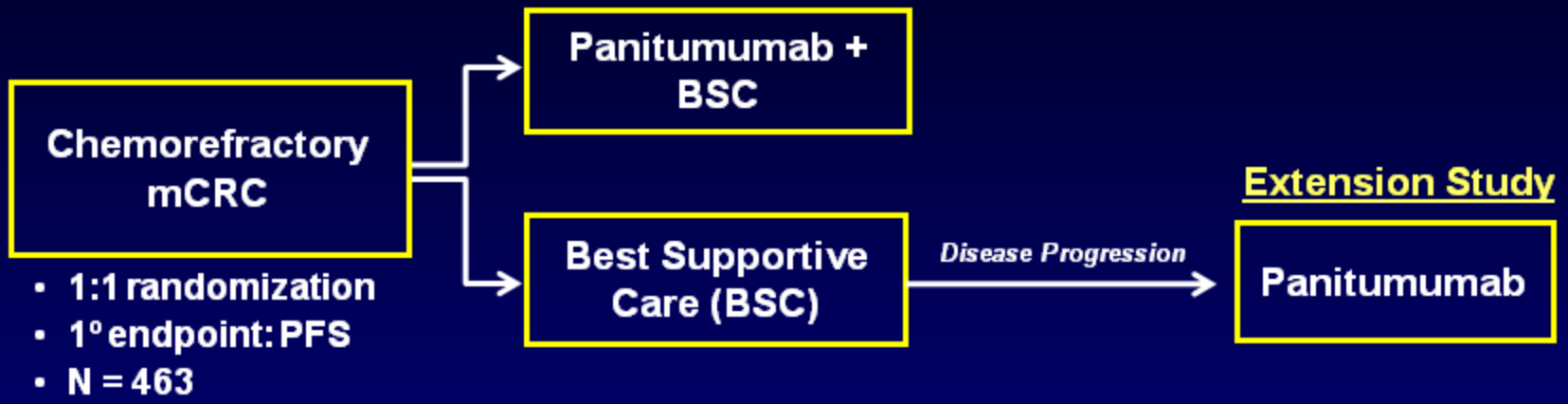
- Vectibix® is a fully human IgG2 monoclonal antibody directed against EGFR
- Accelerated approval was granted in September 2006
- Vectibix® offers an important treatment option for patients with chemorefractory mCRC
  - Indicated as a single agent for the treatment of EGFR-expressing mCRC with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens
- FDA accepted an ongoing study in second-line mCRC as the confirmatory trial (20050181)
- Vectibix® is approved in 37 other countries
  - Indication(s) restricted to patients with wild-type *KRAS* mCRC

Vectibix® (panitumumab) prescribing information, Amgen. Data on File

Status of Post-marketing Commitment (Study 20050181)

December 2005	Study protocol and statistical analysis plan (SAP) submitted for Special Protocol Assessment to FDA
June 2006	First patient enrolled
September 2006	*Accelerated approval of Vectibix®*
December 2007	Amended protocol and SAP *(KRAS)* submitted to FDA
March 2008	Last patient enrolled
October 2010	Final study report for PMC submitted

Accelerated Approval of Vectibix® was Based on Study 20020408



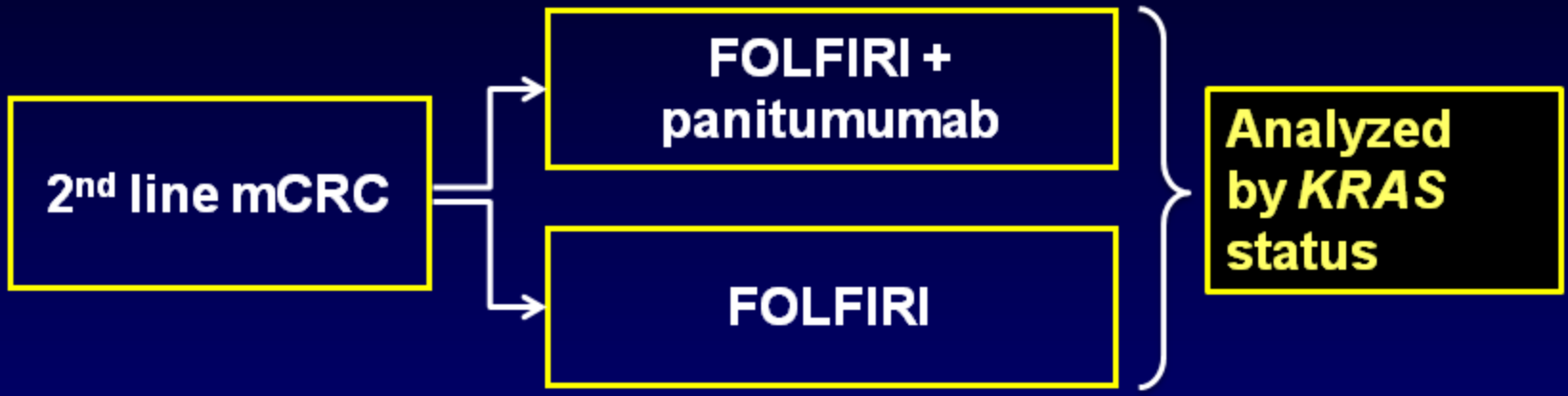
- Study demonstrated an improvement in PFS (HR = 0.54, $P < 0.001$)
- Overall survival was a secondary endpoint and may have been confounded by allowing treatment upon disease progression with anti-EFGR therapy
  - Upon disease progression, 75% of patients in the BSC alone arm received panitumumab in the extension study

1. Van Cutsem E, et al. *J Clin Oncol.* 2007;25(13):1658-64.
2. Vectibix® (panitumumab) prescribing information, Amgen.

Emergence of *KRAS* as a Predictive Biomarker in CRC

- Emerging science demonstrated role of *KRAS* mutations in predicting response to anti-EGFR therapy
- Retrospective analysis of single arm phase 2 studies suggested *KRAS* as a predictive biomarker
- Retrospective analysis (pre-specified analysis plan) of the 20020408 study demonstrated *KRAS* as predictive biomarker (ECCO, September 2007)
- Recognition of importance of *KRAS* status in response to anti-EGFR antibodies (NCCN guidelines updated, October 2008; KRAS ODAC, December 2008)

Confirmatory Trial: FOLFIRI ± Panitumumab (20050181)



- 1:1 randomization
- Co-1º endpoints: PFS & OS
- N = 1,187
- 190 sites, US, EU, AUS, Russia, Japan
- Stratification Factors:
  - Prior oxaliplatin exposure for mCRC
  - Prior bevacizumab exposure for mCRC
  - ECOG performance status (0 or 1 vs. 2)

Peeters M, et al. *J Clin Oncol.* 2010;28(31):4706-13.

Vectibix® Demonstrated Consistent PFS Benefit in Patients with Wild-type *KRAS* mCRC

	Chemorefractory (BSC ± Pmab*) 20020408[1]		Second-line (FOLFIRI ± Pmab*) 20050181[2]		First-line (FOLFOX ± Pmab*) 20050203[3]	
***KRAS* Ascertainment**	92%		91%		93%	
	Pmab* (n = 124)	Control (n = 119)	Pmab* (n = 303)	Control (n = 294)	Pmab* (n = 325)	Control (n = 331)
RR	17%	0%	35%	10 %	55%	48%
PFS Hazard Ratio	0.45 (*P* < 0.001)		0.73 (*P* = 0.004)		0.80 (*P* = 0.02)	
Median PFS (mo)	2.8	1.7	5.9	3.9	9.6	8.0
OS Hazard Ratio	0.99 (*P* = 0.14)		0.85 (*P* = 0.12)		0.83 (*P* = 0.07)	
Median OS (mo)	8.1	7.6	14.5	12.5	23.9	19.7
Subsequent anti-EGFR use in control	77%		31%		18%	

•Pmab = panitumumab

1. Amado R, et al. *J Clin Oncol*.2008;*26:1626-34*, 2. Peeters M, et al. *J Clin Oncol*.2010;27:4706-13, 3.Douillard JY, et al. *J Clin Oncol*. 2010;*27:* 4697-4705

Challenges Encountered

- Discovery of *KRAS* as a biomarker changed the clinical landscape of mCRC
- Lack of availability of a validated KRAS test kit
- Conducting a randomized confirmatory trial when the drug (or drug class) has already demonstrated clinical benefit
  - Study recruitment in regions where the product is not available
  - Inability to blind studies with anti-EGFR agents due to recognized skin toxicities

Questions to be Answered

- Statistically significant benefit in OS has yet to be demonstrated prospectively in patients with wild-type *KRAS* mCRC
  - Frequent use of post-progression anti-EGFR therapy may have confounded the interpretation of OS benefit
  - A study (n~350) of panitumumab versus BSC in patients with chemorefractory wild-type *KRAS* mCRC has been initiated
    - Study offers an opportunity to further evaluate predictive biomarkers (eg, BRAF, NRAS) for panitumumab
- Relative efficacy and safety of cetuximab vs. panitumumab in patients with wild-type *KRAS* mCRC have not been evaluated
  - Amgen is conducting a monotherapy study of cetuximab vs panitumumab (n~1000) in the chemorefractory setting as part of a specific obligation to EMA

Summary

- Accelerated approval of Vectibix® provided an important treatment option for patients with chemorefractory mCRC
- Post-marketing commitments were conducted with due diligence and within agreed upon timelines
- The results of the confirmatory study (20050181) were submitted to FDA on 29 October 2010
- Discovery of *KRAS* as a predictive biomarker redefined use of anti-EGFR monoclonal antibodies in the treatment of mCRC
  - Avoiding toxicity in patients unlikely to benefit
  - Improving benefit:risk in patients with wild-type *KRAS* tumors